Wnt/beta-catenin activation and macrophage induction during liver cancer development following steatosis.

Journal: Oncogene

Publication Year: 2017

Authors: A Debebe, V Medina, C-Y Chen, I M Mahajan, C Jia, D Fu, L He, N Zeng, B W Stiles, C-L Chen, M Wang, K-R Aggarwal, Z Peng, J Huang, J Chen, M Li, T Dong, S Atkins, Z Borok, W Yuan, K Machida, C Ju, M Kahn, D Johnson, B L Stiles

PubMed link: 28671671

Funding Grants: CIRM Stem Cell Biology Training Program, CIRM Stem Cell Biology Training Grant

Public Summary:

Scientific Abstract:
Obesity confers an independent risk for carcinogenesis. In the liver, steatosis often proceeds cancer formation; however, the mechanisms by which steatosis promotes carcinogenesis is unknown. We hypothesize that steatosis alters the microenvironment to promote proliferation of tumor initiating cells (TICs) and carcinogenesis. We used several liver cancer models to address the mechanisms underlying the role of obesity in cancer and verified these findings in patient populations. Using bioinformatics analysis and verified by biochemical assays, we identified that hepatosteatosis resulting from either Pten deletion or transgenic expression of HCV core/NS5A proteins, promotes the activation of Wnt/beta-catenin. We verified that high fat diet lipid accumulation is also capable of inducing Wnt/beta-catenin. Caloric restriction inhibits hepatosteatosis, reduces Wnt/beta-catenin activation and blocks the expansion of TICs leading to complete inhibition of tumorigenesis without affecting the phosphatase and tensin homologue deleted on chromosome 10 (PTEN) loss regulated protein kinase B (AKT) activation. Pharmacological inhibition or loss of the Wnt/beta-catenin signal represses TIC growth in vitro, and decreases the accumulation of TICs in vivo. In human liver cancers, ontology analysis of gene set enrichment analysis (GSEA)-defined Wnt signature genes indicates that Wnt signaling is significantly induced in tumor samples compared with healthy livers. Indeed, Wnt signature genes predict 90% of tumors in a cohort of 558 patient samples. Selective depletion of macrophages leads to reduction of Wnt and suppresses tumor development, suggesting infiltrating macrophages as a key source for steatosis-induced Wnt expression. These data established Wnt/beta-catenin as a novel signal produced by infiltrating macrophages induced by steatosis that promotes growth of tumor progenitor cells, underlying the increased risk of liver tumor development in obese individuals.